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Response Surface Modeling of Ultrasound-Assisted Dispersive Liquid–Liquid Microextraction for Determination of Benzene, Toluene and Xylenes in Water Samples: Box–Behnken Design

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Abstract A simple, fast and effective pre-concentration procedure for the extraction of benzene, toluene and xylenes isomers (BTX) was developed using an ultrasound-assisted dispersive liquid–liquid microextraction coupled with gas chromatography-flame ionization detector in water samples. The effects of different experimental parameters in the extraction step including type and volume of extraction and dispersive solvents, ionic strength, extraction time and sample volume were studied using two techniques, namely one-variable-at-a-time and response surface methodology. The results of "one-variable-at-a-time" showed that the ionic strength and extraction time were not significant on the extraction efficiency. Therefore, a three-factor, three-level Box–Behnken experimental design was employed to optimize the BTX extraction. The optimal conditions were determined to be a volume of extraction solvent (chloroform) of 51 μL, volume of dispersive solvent (methanol) of 514 μL and volume of sample of 12 mL. The enrichment factors of 241.2–305.1, the limit of detections of 205–382 ng L^{-1} were obtained for the BTX at the optimum conditions. In addition, the relative standard deviations for 50 μg L^{-1} of the BTX in the water samples were found to be in the range of 1.9 %–5.7 % (n = 5). The developed procedure was then applied for the extraction and determination of BTX in the water samples.

Keywords BTX · Ultrasound-assisted dispersive liquid–liquid microextraction · Gas chromatography · Response surface methodology · Water samples

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The acronym benzene, toluene and xylenes isomers (BTX)which including a mixture of benzene, toluene and three isomers of xylenes (*ortho*, *meta and para*), are harmful volatile organic compounds (VOCs). The effects of exposure to these substances comprise change in the liver and harmful influences on the kidneys, lungs, heart and nervous system (Aguilera-Herrador et al. 2008). These compounds are emitted to the environment from an extensive source variety including combustion products of wood and fuels, adhesives, industrial paints, aerosols and degreasing agents (Alberici et al. 2002). Therefore, these substances are ubiquitous among the samples of environmental concern (air, soil and water), human exposure to these aromatic hydrocarbons occurring by ingestion (consuming contaminated water or food), inhalation or absorption through the skin. In order to reduce the human intake of these hazardous organic compounds, a chemical control and consequently analysis methods is desirable (Aguilera-Herrador et al. 2008; Carrillo-Carrion et al. 2007). Gas chromatography is the main alternative of choice for the determination of BTX in environmental samples. Although the direct analysis of samples headspace has been traditionally employed for their determination (Aguilera-Herrador et al. 2008; Serrano and Gallego 2004), new extraction strategies including the so-called solventless sample preparation techniques are gaining importance (Lambropoulou et al. 2007), since which they improve the selectivity and sensitivity of the developed methodologies.

Dispersive liquid–liquid microextraction (DLLME) is a pre-concentration method that employs a ternary system of solvents. This technique was reported for the first time in a method for the determination of organophosphorus pesticides in water (Rezaee et al. 2006). However, this method has also been widely used for the extraction and pre-concentration of organic and inorganic compounds (Baliza et al.

2009; Wu et al. 2011; Yan et al. 2011). DLLME is based on the formation of the fine droplets of an extractant in a sample solution when a water-immiscible extraction solvent (extractant) dissolved in a water-miscible organic dispersive solvent rapidly injected into a sample solution. The analytes in the aqueous sample solution are extracted into the fine droplets, which are further separated by centrifugation, and the enriched analytes in the sedimented phase are determined by either spectrometric or chromatographic methods.

The advantages of the DLLME procedure are fast, simplicity of operation, low cost, green extraction procedure (the consumption of organic solvent is reduced to the microliter) and high enrichment factor (Wu et al. 2011).

The aim of this research is to develop a simple, rapid and sensitive ultrasound-assisted dispersive liquid–liquid microextraction (UA-DLLME) procedure coupled with GC-FID for the determination of BTX in water samples. The effect of difference parameters affecting the extraction step including type and volume of extraction and dispersive solvents, extraction time, sample volume and ionic strength were also investigated.

Materials and Methods

A Hewlett-Packard 6890 gas chromatographic (GC) equipped with a 30 m × 0.32 mm i.d. with 0.25 μm stationary film thickness HP-5 capillary column and flame ionization detection (FID) system (Hewlett-Packard, Palo, Alto, CA, USA) was used for all analyses. The injector and detector temperatures were 250 and 300°C, respectively. The all injections were made in the splitless mode. The column was initially maintained at 60°C for 2 min; subsequently, the temperature was increased to 135°C at a rate of 10°C min^{-1}, then it was increased to 260°C at 30°C min^{-1}, then held at 260°C for 5 min.

Benzene, toluene, *o*-xylene, *m*-xylene, *p*-xylene, acetonitrile, chloroform, methanol, dichloromethane and acetone were obtained from Merck (Darmstadt, Germany). A stock standard solution of BTX (1,000 μg mL^{-1}) was prepared in methanol. It was then stored in a refrigerator at 4°C. The fresh working solutions were prepared daily in double distilled water by diluting the stock solution.

The tap, well, river, mineral and waste water were collected in amber-glass bottles without headspace. The samples were store in the refrigerator at 4°C until their analysis.

10 mL of water sample was placed in a 20.0 mL conic tube and fortified with the BTX mixture at the concentration level of 500 μg L^{-1}. Then, the mixture of 0.5 mL of methanol (as disperser solvent) containing 100 μL of chloroform (as extraction solvent) was rapidly injected into the sample solution by syringe. The mixture solution was gently shaken and ultrasonicated for 2 min to form a homogeneous cloudy solution. The mixture solution was then centrifuged at 4,000 rpm for 5.0 min, causing the sedimentation of the solvent droplets in the bottom of the conical test tube. The volume of settled organic phase was measured using a 10 μL Hamilton microsyringe (Reno, Nevada, USA). A 1-μL volume of sedimented phase was injected into the GC.

Results and Discussion

The factors affecting the extraction efficiency including nature and volume of extraction and dispersive solvent, ionic strength and extraction time were optimized. The optimization was performed on water solution of 500 μg L^{-1} for each BTX compounds. The chromatographic peak area, which is related to the number of moles of analytes that are extracted into the extraction organic solvent, was used to evaluate the extraction efficiency under different experimental conditions.

To establish a UA-DLLME technique, it is necessary to select a proper extraction organic solvent. The choice of extraction solvent needs the following considerations: lower/higher density than water, low solubility in water such as to prevent the dissolution in the aqueous phase, good affinity for target compounds, good chromatographic behavior and also it must be miscible in the dispersive solvent. Chloroform, dichloromethane, *n*-hexane and *n*-heptane were selected as extraction solvents. A sample solution (100 μL of each solvent in 0.5 mL of methanol as dispersive solvent) was used for optimization. The experimental results showed that, among the solvents tested, only chloroform had higher peak area. Therefore, it was selected as the extracting solvent.

For this method, the dispersive solvent should be miscible with the extraction solvent as well as the aqueous phase. Appropriate dispersive solvent can disperse the extraction solvent to fine droplets in water sample and increases the surface area for transferring the analyte compounds from sample matrix to extraction solvent. Several solvents including methanol, acetonitrile and acetone were used as dispersive solvents to investigate their influence on the extraction efficiency. The best peak area was obtained by using methanol as dispersive solvent. Therefore, methanol was selected as dispersive solvent for next experiments.

To study the effect of the volume of extracting solvent on the extraction efficiency, the solution containing various volumes of chloroform (30, 60, 90, 120 and 150 μL) were subjected to the UA-DLLME method. The results are shown in Fig. 1. By increasing the volume of chloroform, the peak area were first increased to 60 μL for all target compounds, and then decreased for all the analytes. At higher volumes of chloroform due to increasing of sedimented phase volume and dilution of the BTX, GC peak

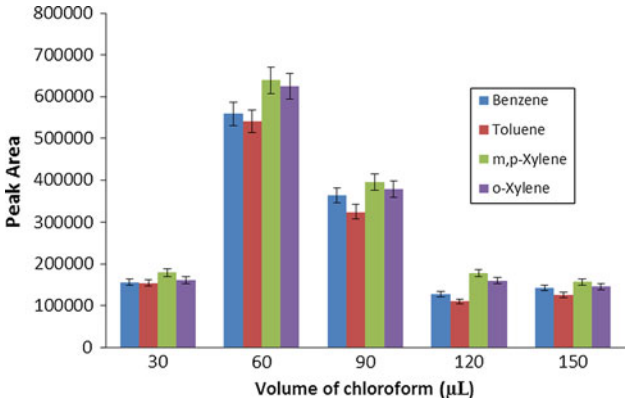

Fig. 1 Study of volume of chloroform effect on the peak area BTX in UA-DLLME

areas of the analytes were decreased. Therefore, 60 µL of chloroform were used in subsequent experiments.

For the optimization of the volume of dispersive volume, the experiments were carried out by using different volumes of the dispersive solvent methanol (0.2, 0.5, 0.75 and 1.0 mL). As shown in Fig. 2, the peak area increases first for all compounds and then decreases by increasing the volume of methanol for all the BTX. The reason could be explained that at a low methanol volume, a cloudy state could not be well formed; therefore, the peak area is low. At a higher methanol volume, the solubility of the BTX in water was increased, thereby; the peak area was decreased due to the decrease of distribution coefficient (Wu et al. 2011). Therefore, based on the experimental results, 0.5 mL of methanol was chosen for subsequent studies.

In traditional LLE, the extraction time is very important and expected to affect the extraction efficiency. The formation of the ternary emulsion is a key step in DLLME that affects the area of contact between the extraction solvent and aqueous phase and finally affects the extraction efficiency

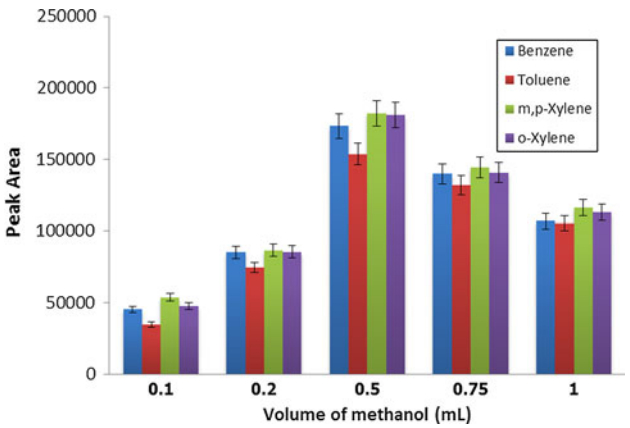

Fig. 2 Study of volume of methanol effect on the peak area BTX in UA-DLLME

(peak area). Thus, an ultrasound-assisted technique was adopted to accelerate the formation of homogenous cloudy solution. Therefore, the effect of extraction time, in the range of 1–10 min was examined in this study. The results revealed the quantitative extraction (>97 % for all analytes) was obtained in 2 min, therefore, the extraction time has no significant effect on the extraction efficiency. It is obvious that the surface area between the aqueous phase and extraction solvent chloroform is very large. Therefore, transition of the target compounds from the aqueous phase to the chloroform is fast. This is the most important advantage of DLLME. Thus, based on the experimental results, 2 min extraction time was chosen for subsequent studies. The effect of NaCl concentration in the range of 0.1–1.0 mol L^{-1} was also investigated as a salting agent, the extraction efficiency was quantitative (>97 %) for all analytes in the absence of salt, therefore, the NaCl concentration had no significant effect on the extraction efficiency of target compounds.

The three-levels, three factorial Box–Behnken experimental design was used to investigate the process parameters affecting the extraction of BTX. The input variables were chloroform volume (V_c) (30–90 µL), methanol volume (V_m) (500–1,000 µL) and sample volume (V_s) (5–15 mL). The factor levels were coded as −1 (low), 0 (central point) and 1 (high). Table 1 shows the design of real experiments of Box–Behnken.

The behavior of the system is explained by the following quadratic equation (Sharma et al. 2008).

$$Y = \beta_0 + \sum \beta_i \chi_i + \sum \beta_{ii} \chi_{ii}^2 + \sum \beta_{ij} \chi_i \chi_j + \varepsilon \quad (1)$$

where Y is the process response or output (dependent variable), β_0 is the constant, x_1, x_2,…, x_k are the coded independent variables, β_i is the linear effect, β_{ii} is the quadratic effect, β_{ij} is the interaction effect, and ε is the random error or allows for description or uncertainties between predicted and measured value.

A multiple function (multiple responses, R_m) was used to evaluate the effects of the main parameters quadratic, and their interactions. This was calculated as follows, taking the first run as an example (Gaujac et al. 2008):

$$R_m = \frac{19102}{30868} + \frac{25400}{27313} + \frac{48834}{61930} + \frac{51705}{75682} = 3.02 \quad (2)$$

The multiple response model generated by the execution of the Box–Behnken experimental design can be described by:

$$\begin{aligned} Y = &- 7.21875 + 0.06843(V_c) + 0.014(V_m) \\ &+ 0.90058(V_s) - 0.00055(V_c)^2 - 0.00001(V_m)^2 \\ &- 0.03072(V_s)^2 - 0.00001(V_c)(V_m) \\ &- 0.00062(V_c)(V_s) - 0.00027(V_m)(V_s) \end{aligned} \quad (3)$$

The critical point in the surface response are founded by solving this equation system for the condition of

Table 1 Matrix for the Box–Behnken experimental design

No.	V_c (μL)	V_m (μL)	V_s (mL)	Peak area					
				Benzene	Toluene	*m*, *p*-Xylene	*o*-Xylene	Observed, R_m	Predicted, R_m
1	30	500	10	19102	25400	48834	51705	3.02	3.02
2	90	500	10	17062	19465	38403	43563	2.46	2.52
3	30	1000	10	30868	15309	41639	50025	2.89	2.83
4	90	1000	10	8409	24722	35701	20521	2.03	2.03
5	30	750	5	6090	20741	52345	29378	2.19	2.22
6	90	750	5	1211	21005	45226	17483	1.77	1.75
7	30	750	15	20714	24311	42602	46465	2.86	2.89
8	90	750	15	5613	23780	30959	39126	2.07	2.04
9	60	500	5	7326	20503	51723	9477	1.95	1.92
10	60	1000	5	16948	12727	52709	26965	2.22	2.25
11	60	500	15	28676	18186	31335	75682	3.1	3.07
12	60	1000	15	16728	21632	24657	22400	2.03	2.06
13	60	750	10	24303	26956	61930	61885	3.59	3.48
14	60	750	10	22153	27313	58958	54965	3.4	3.48
15	60	750	10	23116	25865	60875	59285	3.46	3.48

$\frac{\delta(Y)}{\delta(V_c)} = 0$, $\frac{\delta(Y)}{\delta(V_m)} = 0$ and $\frac{\delta(Y)}{\delta(V_s)} = 0$. The way of calculating these critical points has been published in previous study (Santos et al. 2004). The calculated values for the critical point are as follows: chloroform volume = 51.0 μL; methanol volume = 514.0 μL and sample volume = 12 mL.

The percent contribution (PC%) of each of the individual term in final model were computed (Table 2) using the SS values of the corresponding term (Eq. 4) (Yetilmezsoy et al. 2009).

$$PC = \frac{SS}{\sum SS} \times 100 \quad (4)$$

Table 2 shows the results of the response surface model fitting in the form of analysis of variance (ANOVA). The ANOVA results suggest that the model was significant, as evident from the Fisher's *F* test ($F_{model} = 92.86$) with a very low probability value ($p_{model} = < 0.0001$). Therefore, the calculated *F* value was compared with the critical *F* value ($F_{\alpha,df,(n-df+1)} = F_{0.05,9,5} = F_{tab} = 4.77$) for the considered probability ($p = 0.05$). The results show that the critical *F* value is very less than the calculated *F* values of 92.86. The results suggest that the computed Fisher's variance ratio at this level was large enough to justify a very high degree of adequacy of the quadratic model and significance of the variables combinations (Yetilmezsoy et al. 2009). The goodness of fit of the model was checked by the correlation coefficient (R^2). The adjusted R^2 value (0.983) showed that only 1.7 % of the total variation was

Table 2 ANOVA analysis for multiple response function

Source	Sum of squares	*df*	Mean of square	*F* value	*p* value	(PC%)[a]
Model	5.280	9	0.587	92.86	< 0.0001	–
V_c	0.547	1	0.547	86.53	0.0002	6.77
V_m	0.754	1	0.754	119.35	0.0001	9.34
V_s	2.630	1	2.630	416.32	< 0.0001	32.57
(V_c) (V_m)	0.023	1	0.023	3.56	0.1178	0.28
(V_c) (V_s)	0.034	1	0.034	5.42	0.0674	0.42
(V_m) (V_s)	0.449	1	0.449	71.05	0.0004	5.56
$(V_c)^2$	0.897	1	0.897	141.98	< 0.0001	11.11
$(V_m)^2$	0.563	1	0.563	89.07	0.0002	6.97
$(V_s)^2$	2.177	1	2.177	344.61	< 0.0001	26.96
Residual	0.032	5	0.006			
Lack of Fit	0.013	3	0.004	0.45	0.7444	
Pure Error	0.019	2	0.009			

[a] Percentage contribution (%)

not explained by this model. Therefore, the value of correlation coefficient ($R^2 = 0.994$) indicates good relation between the experimental and predicted values of the response. The lack-of-fit measures the failure of the model to represent data in the experimental domain at points which are not included in the regression (Yetilmezsoy et al. 2009). The non-significant value of lack-of-fit (>0.05) revealed that the quadratic model is statistically significant for the response.

The figures of merit of the proposed procedure were summarized in Table 3. The calibration graphs were drawn using ten spiking levels working of all the analytes at different concentration in the range from 0.005–25 μg mL^{-1}.

The extraction conditions were as follows: sample solution: 12 mL, chloroform volume (extraction solvent): 60 μL and methanol volume (dispersive solvent): 0.5 mL. In the present procedure, peak area was used as analytical signal. Good linear relationships between the corresponding peak areas and the concentration for all the analytes were obtained ($r^2 > 0.999$). The repeatability of the proposed procedure, expressed as relative standard deviation

Table 3 Figures of merit of the proposed method

Compound	r^2	LOD[a]	Linear range (μg mL^{-1})	RSD%	Enrichment factor
Benzene	0.9995	205	0.005–25	2.1	241.2
Toluene	0.9992	302	0.005–25	3.2	235.7
m + *p*-Xylene	0.9991	255	0.005–25	3.5	305.1
o-Xylene	0.9997	273	0.005–25	2.9	295.4

[a] LOD, limit of detection in ng L^{-1}

Table 4 Determination of the BTX (μg L^{-1}) in different water samples

Sample	Benzene	Toluene	*m* + *p*-Xylene	*o*-Xylene
Tap water				
Non-spiked	–	–	–	–
Spiked[a]	49.25 ± 2.6[b]	49.45 ± 1.9	48.4 ± 3.4	48.25 ± 3.7
Recovery (%)	98.5	98.9	96.8	96.5
Spiked[c]	3.05 ± 2.1	2.95 ± 2.3	2.93 ± 3.8	3.02 ± 2.7
Recovery (%)	101.5	98.3	97.6	100.6
Well water				
Non-spiked	–	–	–	–
Spiked[a]	48.6 ± 4.8	48.05 ± 4.1	47.65 ± 4.9	48.45 ± 3.2
Recovery (%)	97.2	96.1	95.3	96.9
Spiked[c]	3.03 ± 5.1	3.1 ± 4.5	2.89 ± 3.9	2.93 ± 4.4
Recovery (%)	101.0	103.3	96.3	97.6
River water				
Non-spiked	–	–	–	–
Spiked[a]	51.25 ± 3.4	48.55 ± 5.7	50.65 ± 2.9	47.4 ± 5.5
Recovery (%)	102.5	97.1	101.3	94.8
Spiked[c]	2.91 ± 3.1	2.95 ± 4.2	3.1 ± 4.9	2.96 ± 3.8
Recovery (%)	97.0	98.3	103.3	98.6
Mineral water				
Non-spiked	–	–	–	–
Spiked[a]	47.8 ± 5.4	48.05 ± 4.9	51.7 ± 5.1	51.05 ± 3.2
Recovery (%)	95.6	96.1	103.4	102.1
Spiked[c]	2.93 ± 5.1	2.89 ± 4.5	2.95 ± 3.7	2.94 ± 4.4
Recovery (%)	97.6	96.3	98.3	98.0
Waste water[d]				
Non-spiked	3.3 ± 5.1	4.1 ± 5.3	3.7 ± 4.8	3.5 ± 4.5
Spiked[a]	53.95 ± 3.8	55.45 ± 5.3	52.35 ± 4.7	51.75 ± 4.3
Recovery (%)	101.3	102.7	97.3	96.5
Spiked[c]	6.22 ± 4.5	7.01 ± 4.1	6.6 ± 4.8	6.44 ± 5.1
Recovery (%)	97.4	97.1	96.7	98.0

[a] 50.0 μg L^{-1} of the BTX were added to 5.0 mL of different water samples

[b] RSD%

[c] 3.0 μg L^{-1} of the BTX were added to 5.0 mL of different water samples

[d] This water was collected from near the gas station

Table 5 Comparison of the UA-DLLME–GC-FID procedure with other related methods for determination of BTX

Extraction method	Detection	LOD (ng mL^{-1})	RSD%	Reference
SPME	GC-FID	0.2–1.0	4.0–8.0	Florez Menendez et al. (2000)
HF-LPME	GC-FID	7.0–30.0	2.02–4.61	Sarafraz-Yazdi et al. (2008)
DI-SDME	GC-FID	7.2–16.5	10.6–12.2	Wang et al. (2006)
UA-DLLME	GC-FID	0.2–0.4	1.9–5.7	This study

(RSD%) was obtained using extracting five consecutive aqueous samples (spiked at 0.1 μg mL^{-1} with all of the analytes) an was found to vary between 2.1 % and 3.5 %. The limit of detection (LOD), calculated as concentration equivalent to three times of standard deviation of the blank, was in the range 0.205–0.382 μg L^{-1} for different BTX. The enrichment factor of BTX, calculated as the ratio of the final concentration of target compound in the sedimented phase and its concentration in the initial solution, was obtained in the range of 241.2–305.1.

To evaluate the accuracy and applicability of the proposed procedure (UA-DLLME) for real water samples, the extraction and determination of the BTX in various water samples were carried out. To assess the effects of matrix, the water samples were spiked with BTX at a concentration of 50 and 3 μg L^{-1}. Table 4 shows that the results of five replicate analysis of each water samples obtained by UA-DLLME procedure.

The results of the present study showed that the separation and pre-concentration of BTX in water samples could be carried out by using UA-DLLMA prior to analysis by GC-FID. Comparison of this procedure with other methods (Table 5) demonstrated that UA-DLLME procedure has good limit of detection. Furthermore, this procedure is easy, inexpensive and highly sensitive with low limit of detection. The environmental pollution of this method is limited because a very small amount of organic solvent was used, thereby; its particularly attractive due to the "green chemistry" concept could be employed here. As an overall conclusion, this procedure possesses good potential in the analysis of ultra-trace compounds in real samples.

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